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A Short Path to Erythrina Alkaloid Derivatives

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Erythrina alkaloids which display a variety of biological activity including hypnotic and CNS activity[1] have drawn attraction for the synthesis over the years. Some of the recent strategies on the construction of the core spirocyclic structure include intramolecular cyclization reactions such as radical cyclizations,[2] electrophilic substitution cyclizations on *N*-acyliminium intermediates or Pummerer-induced cyclizations,[3] Heck reactions,[4] and anionic substitution reactions.[5]

A few years ago, we developed a new route to the spirocyclic skeleton by palladium-catalyzed arylation of α,β-unsaturated γ-lactam.[6] In the route, the precursors for cyclization have been prepared by condensation of arylamine and keto-ester intermediates[3c] under reflux in toluene in the presence of TsOH (Scheme 1).[3d]

For the synthetic application of this method toward erythrina alkaloids, we wanted to reinvestigate the palladium catalyzed cyclization of the requsite precursor which would be formed from the condensation of ketoester **1** and bromo-arylamine **2**. In the reaction, two main products were formed as shown in the Scheme 2, and the separated yields were 34% of compound **3** and 18% of compound **4**. For the selective formation of each isomer, we have tried the cyclization reaction under different conditions by changing solvent, catalyst, and temperature. However, the ratio did not shift favorably for the purpose, so we considered that we had better find ways to transform each isomer to proper natural products or derivatives. It was envisioned that major intermediate **3** would be a proper precursor for erysotramidine and the minor intermediate **4** for iso-13-demethoxyerythratidinone (Scheme 2).

When the intermediate **3** was treated with $Pd(OAc)_2$ in DBU, enol intermediate was formed in 30% yield through γ-lactam enolate formation followed by cyclization. Some amount of the corresponding ketal compound, the precursor of the enol intermediate, could be obtained if the reaction process was quenched earlier. However, the ketal interemediate was found to be reluctant to hydrolyse to ketone. Treatment of **5** with

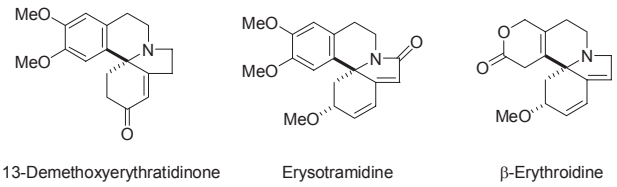
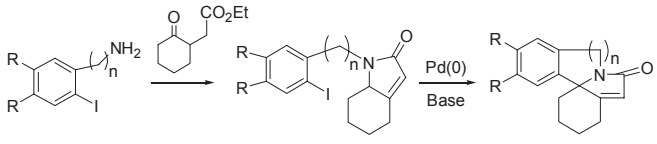
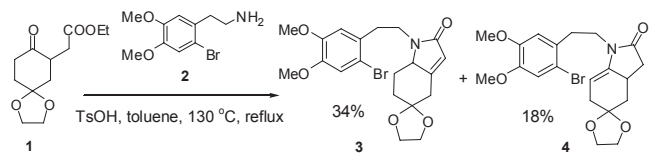


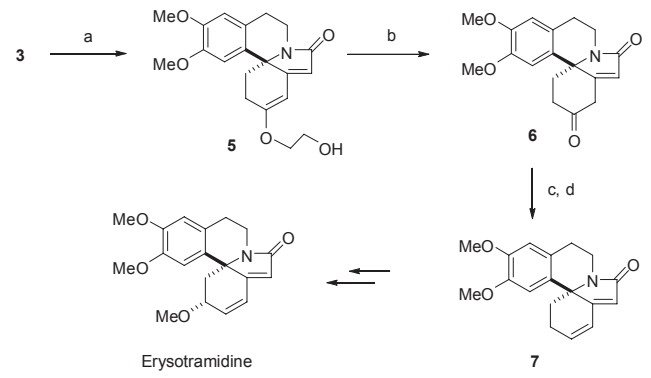
Figure 1



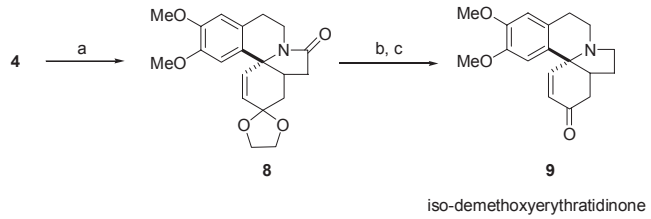
Scheme 1



Scheme 2



Scheme 3. Reagents and conditions (a) $Pd(OAc)_2$, DBU, 140 °C, 15 h, 30%; (b) TsOH, acetone, reflux, 6h, 71%; (c) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 3 h, dr 2.6:1; (d) $POCl_3$, DBU, CH_2Cl_2, 3 h, 64% (2 steps)



Scheme 4. Reagents and conditions (a) $Pd(OAc)_2$, PPh_3, DBU, 140 °C, 15 h, 87%; (b) $LiAlH_4$-$AlCl_3$, THF; (c) TsOH, acetone, 80 °C, 2 h, 80% (2 steps)

TsOH in acetone afforded compound **6** in 71% yield. Reduction of the carbonyl compound **6** under Luche condition, affording a mixture of diasteromers in 2.6 : 1 ratio, was followed by elimination to afford the known intermediate **7** for erysotramidine in 64% yield (Scheme 3).[7]

Meanwhile, intermediate **4** was subjected to the conventional Heck reaction, yielding the 6-membered quaternary structure **8** in 87% yield rather than 7-membered ring compound. Reduction of the amide group of **8** by LAH/$AlCl_3$ to amine was followed by deprotection of ketal under acid to iso-13-demethoxyerythratidinone[8] in 80% in two steps.

In conclusion, we have prepared two intermediates from condensation of compound **1** and 2, and suggested concise routes to the synthesis of erysotramidine and iso-13-demethoxyerythratidinone through Pd-mediated cyclization of the intermediates.

Experimental Section

1'-(2-Bromo-4,5-dimethoxyphenethyl)-1',6',7',7a'-tetrahydrospiro[[1,3]dioxolane-2,5'-indol]-2'(4'*H*)-one (3) and 1'-(2-bromo-4,5-dimethoxyphenethyl)-3',3a',4',6'-tetrahydrospiro[[1,3]dioxolane-2,5'-indol]-2'(1'*H*)-one (4). To a solution of **1** (2 g, 8.25 mmol) in anhydrous toluene (30 mL) were added TsOH (314 mg, 1.65 mmol) and 2-(2-bromo-4,5-dimethoxyphenyl)ethanamine **2** (2.36 g, 9.08 mmol). The reaction mixture was refluxed for 15 h using Dean-Stark trap. The solvent was evaporated under reduced pressure and the resultant crude material was purified by silica gel column chromatography with *n*-hexane/EtOAc (1:1 to 1:3), EtOAc 100% and EtOAc/MeOH (20:1) to give **3** (1.23 g, 34%) and **4** (651 mg, 18%).

Compound 3: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.99 (1H, s), 6.76 (1H, s), 4.91 (1H, m), 4.06-3.92 (4H, m), 3.86 (3H, s, OMe), 3.85 (3H, s, OMe), 3.76 (1H, m), 3.50 (1H, m), 3.15-2.82 (3H, m), 2.58 (1H, dd, J = 6.8, 16.4 Hz), 2.50-2.32 (2H, m), 2.17 (1H, dd, J = 10.4, 16.4 Hz), 2.06 (1H, dd, J = 4.8, 12.4 Hz), 1.64 (1H, t, J = 12,4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.1, 148.3, 148.1, 141.1, 129.6, 115.2, 113.9, 113.2, 107.8, 94.1, 64.3, 64.1, 55.9, 55.8, 39.4, 36.5, 36.1, 34.6, 32.9, 32.6.

Compound 4: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.00 (1H, s), 6.81 (1H, s), 5.85 (1H, s), 4.05-3.89 (4H, m), 3.85 (3H, s, OMe), 3.84 (3H, s, OMe), 3.67 (1H, dd, J = 6.0, 12.0 Hz), 3.40 (1H, m), 2.92 (3H, m), 2.81 (1H, dd, J = 2.4, 14.0 Hz), 2.53 (1H, dd, J = 2.0, 14.0 Hz), 2.35 (1H, m), 1.85 (1H, m), 1.71 (1H, ddd, J = 3.6, 14.0, 17.6 Hz), 1.27 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.4, 158.3, 148.5, 148.2, 129.9, 120.7, 115.4, 113.9, 113.5, 109.5, 64.8, 64.6, 61.5, 56.1, 40.1, 38.2, 34.8, 27.7.

(*S*)-3-(2-Hydroxyethoxy)-1,2,8,9-tetrahydro-11,12-dimethoxyindolo[1-a]isoquinolin-6-one (5). A mixture of **2** (548 mg, 1.25 mmol) and $Pd(OAc)_2$ (14 mg, 0.063 mmol) in 5 mL DBU in a sealed tube was heated at 140 °C for 15 h. The reaction mixture was quenched with 40 mL aqueous HCl 2M solution, and then extracted with CH_2Cl_2 (30 mL × 3). The organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (EtOAc/MeOH 20:1 to 10:1) to afford **5** (132 mg, 30%) as a brownish liquid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.0 (1H, s), 6.71 (1H, s), 5.96 (1H, s), 5.73 (1H, s), 4.15-3.91 (5H, m), 3.85 (3H, s, OMe), 3.75 (3H, s, OMe), 3.56 (1H, m), 2.98 (2H, m), 2.41-2.25 (2H, m), 1.90 (1H, m), 1.79-1.61 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.2, 163.6, 159.4, 148.1, 146.6, 128.7, 126.5, 115.0, 112.0, 108.4, 95.4, 69.5, 64.5, 60.7, 55.9, 55.8, 37.3, 33.4, 27.0, 26.9.

(*S*)-1,2,8,9-Tetrahydro-11,12-dimethoxy-4*H*-indolo[1-a]isoquinoline-3,6-dione (6). A solution of **5** (132 mg, 0.37 mmol) and TsOH (10 mg) in acetone (10 mL) was refluxed at 60 °C for 6 h. The reaction mixture was concentrated in vacuo and the resultant residue was purified by silica gel column chromatography with EtOAc 100% to yield compound **6** (82 mg, 71%) as a yellowish liquid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.70 (1H, s), 6.55 (1H, s), 6.25 (1H, s), 4.33 (1H, ddd, J = 4.0, 8.4, 13.6 Hz), 3.86 (3H, s, OMe), 3.77 (3H, s, OMe), 3.42 (1H, dt, J = 8.0, 13.6 Hz), 3.22 (2H, s), 3.11 (1H, dt, J = 8.4, 16.8 Hz), (1H, m), 2.90 (1H, ddd, J = 4.0, 8.0, 16.8 Hz), 2.58-2.52 (2H, m), 2.48 (1H, m), 2.34 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 197.4, 170.2, 158.3, 149.1, 146.9, 126.3, 126.1, 125.3, 113.3, 108.0, 63.8, 56.1, 56.0, 37.0, 35.1, 34.9, 33.6, 25.6.

(*S*)-1,2,8,9-Tetrahydro-11,12-dimethoxyindolo[1-a]isoquinolin-6-one (7). To a solution of **6** (82 mg, 0.26 mmol) in anhydrous MeOH was added $CeCl_3.7H_2O$ (108 mg, 0.29 mmol). The mixture was stirred for 30 min before the addition of $NaBH_4$ (11 mg, 0.29 mmol). After 3 h, the reaction mixture was extracted with EtOAc (30 mL × 3), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was dissolved in anhydrous CH_2Cl_2 (4 mL) followed by addition of $POCl_3$ (29 μL, 0.31 mmol) and DBU (191 μL, 1.3 mmol) consecutively. After 3 h, the reaction mixture was evaporated under reduced pressure and purified by silica gel column chromatography (EtOAc/MeOH 30:1 to 15:1) to give **7** (51 mg, 64%) as a colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.01 (1H, s), 6.82 (1H, dd, J = 2.8, 10 Hz), 6.70 (1H, s), 6.30 (1H, m), 5.89 (1H, s), 4.04 (1H, dt, J = 7.2, 12.8 Hz), 3.86 (3H, s, OMe), 3.77 (3H, s, OMe), 3.56 (1H, dt, J = 6.8, 12.8 Hz), 2.99 (2H, t, J = 6.8 Hz), 2.42 (1H, dt, J = 5.6, 19.2 Hz), 2.33 (1H, dd, J = 4.8, 12.4 Hz), 2.21 (1H, m), 1.85 (1H, dt, J = 5.6, 12.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.2, 157.9, 148.2, 146.8, 136.0, 128.7, 126.3, 124.0, 118.9, 112.1, 108.7, 64.6, 56.0, 55.9, 37.0, 35.0, 27.2, 24.6.

11',12'-Dimethoxy-4a',5',8',9'-tetrahydrospiro[[1,3]dioxolane-2,3'-indolo[1-a]isoquinolin]-6'(4'*H*)-one (8). A mixture of **4** (173 mg, 0.4 mmol), PPh_3 (21 mg, 0.08 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol) and DBU (3 mL) in a sealed tube was heated at 140 °C for 15 h. The reaction mixture was treated with aqueous HCl 2M solution until pH = 2, then extracted with $CHCl_3$ (30 mL × 3), dried over anhydrous Na_2SO4 and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (EtOAc/MeOH 20:1 to 10:1) to afford **8** (124 mg, 87%) as a colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.78 (1H, s), 6.59 (1H, s), 5.85 (1H, d, J = 10.4 Hz), 5.77 (1H, d, J = 10.4 Hz), 4.35 (1H, m), 4.12-3.97 (4H, m), 3.86 (3H, s, OMe), 3.85 (3H, s, OMe), 3.06-2.83 (3H, m), 2.68-2.60 (2H, m), 2.49-2.39 (2H, m), 2.09 (1H, dd, J = 4.8, 14.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.9, 148.2, 147.9, 131.0, 130.3, 126.7, 126.2, 111.9, 109.3, 103.2, 64.9, 64.3, 61.1, 56.0, 55.9, 39.1, 36.1, 35.1, 34.1, 28.6.

Iso-demethoxyerythratidinone (9). To a solution of anhydrous $AlCl_3$ (60 mg, 0.45 mmol) in anhydrous THF (2 mL) at 0 °C was added 1,5 mL solution of $LiAlH_4$ 1M in THF. This solution

was added *via* cannula to a solution of **8** (100 mg, 0.28 mmol) in THF (3 mL) at 0 °C. The reaction mixture was quenched with ice-water after 1 h, and extracted with $CHCl_3$ (20 mL × 3), dried over anhydrous Na_2SO_4 and concentrated in vacuo to give the crude product: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.87 (1H, s), 6.55 (1H, s), 5.83 (1H, d, J = 12.0 Hz), 5.69 (1H, d, J = 12.0 Hz), 4.09-3.95 (4H, m), 3.85 (3H, s, OMe), 3.84 (3H, s, OMe), 3.18-3.11 (3H, m), 3.01-2.90 (2H, m), 2.62 (1H, m), 2.48 (1H, m), 2.12 (1H, dd, J = 5.2, 13.6 Hz), 2.04 (1H, dd, J = 8.4, 13.6 Hz), 1.95 (1H, m), 1.81 (1H, m). The crude product was dissolved in acetone (5 mL) followed by addition of 10 mg of TsOH. The reaction solution was heated at 80 °C for 2 h, and then concent rated under reduced pressure. The resulting residue was purified by silica gel column chromatography ($CHCl_3$/MeOH 20:1 to 10:1) to yield **9** (67 mg, 80%) as a colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.69 (1H, s), 6.68 (1H, s), 6.58 (1H, dd, J = 2.0, 10.4 Hz), 6.04 (1H, d, J = 10.4 Hz), 3.88 (3H, s, OMe), 3.80 (3H, s, OMe), 3.17-2.84 (6H, m), 2.66-2.52 (2H, m), 2.07 (1H, m), 1.74-1.63 (2H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 198.6, 151.9, 147.9, 147.6, 129.1, 127.5, 125.

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